REMARKS/ARGUMENTS

Claims 25-26 and 29-36 are pending in this application and presented for Examination. Claims 25, 26, 29, and 32-34 have been amended. No new matter has been introduced with the foregoing claim amendments. Reconsideration is respectfully requested.

Applicants have amended claims 25, 26, 29, and 32-34 by making minor changes to the formatting and claim language to make it easier to read. No new matter has been introduced with the foregoing changes and Applicants respectfully request that they be entered.

I. REJECTION UNDER 35 U.S.C. § 103(a)

The Examiner has rejected claims 25-26 and 29-31 under 35 U.S.C. § 103(a) as allegedly being obvious over Targan *et al.* in view of Vasiliauskas *et al.* and Landers *et al.* In response, Applicants respectfully traverse the rejection.

The Examiner states:

> Targan et al. describes a sub-type of Crohn's disease patients: those patients whose Crohn's disease is associated with antibodies to bacteria (OmpC and I2 antibodies) who would benefit from antibiotics to kill those bacteria. Whether the Targan, et al. reference conclusively determines a correlation between seroreactivity and the likelihood of success for a particular antibiotic therapy is not persuasive. Targan et al. is being relied on simply for it's teaching that a subset of Crohn's disease patients has the serological markers I2 and OmpC. Applicant's argument that unlike the cited reference, the present invention describes these markers in relation to their associations with specific Crohn's Disease subgroups, such as fibrostenosis is not persuasive. Vasiliauskas et al teaches detecting ASCA and ANCA antibodies as a tool to stratify Crohn's disease into immunologically homogenous subgroups with distinct characteristic including fibrostenosis, internal perforating disease and the need for small bowel surgery.

As set forth in M.P.E.P. § 2141 (I), the Patent Office's policy is to follow *Graham v. John Deere Co. of Kansas City*, 383 U.S. 1 (1966), in the consideration and determination of

obviousness under 35 U.S.C. § 103. The four factual inquiries enunciated in *Graham* for determining obviousness are as follows:

(A) Determining the scope and contents of the prior art;

(B) Ascertaining the differences between the prior art and the claims in issue;

(C) Resolving the level of ordinary skill in the pertinent art; and

(D) Evaluating evidence of secondary considerations.

Recently, the U.S. Supreme Court affirmed the holding of *Graham* regarding obviousness. *See, KSR Int'l Co. v. Teleflex Inc.*, 127 S.Ct. 1727 (2007).

To establish a *prima facie* case of obviousness, three basic criteria must be met: (1) there must be some suggestion or motivation, either in the references themselves or in the knowledge generally available to one of ordinary skill in the art, to modify the reference or to combine reference teachings; (2) there must be a reasonable expectation of success; and (3) the cited art must teach or suggest all the claim limitations. *See,* M.P.E.P. § 2143.

With respect to the present rejection, the Examiner alleges that Targan *et al.* is being relied on simply for it's teaching that a subset of Crohn's disease patients has serological markers I2 and OmpC. With respect to Vasiliauskas *et al.*, the Examiner states that this reference teaches detecting ASCA and ANCA antibodies as a tool to stratify Crohn's disease into immunologically homogenous subgroups with distinct characteristics including fibrostenosis, internal perforating disease and the need for small bowel surgery. The Examiner is of the opinion that one of ordinary skill in the art at the time of invention would have further combined the OmpC and I2 markers to further stratify the fibrostenotic subgroups, especially given the fact that some types of Crohn's disease are associated with other bacterial markers as taught by Targan *et al.* and Landers *et al.* In response, Applicants respectfully disagree.

A. Biomarkers

The current claims are drawn to *diagnostic methods* for determining a risk of having or developing a clinical subtype of Crohn's disease. In contrast, Targan *et al.* teach the use of I2 and OmpC in assessing the likelihood of achieving *efficacy* in subjects with Crohn's disease with *antibiotic* therapy. The currently claimed method is much different than the art cited by the Examiner. In the claimed methods, the magnitude of IgA anti-I2 antibodies, anti-*Saccharomyces cerevisiae* antibodies (ASCA), and IgA anti-OmpC antibodies are measured and the risk of a subject is stratified using the foregoing measurements. The *efficacy* of antibiotic treatment as taught by Targan *et al.* has nothing at all to do with the claimed methods.

Vasiliauskas *et al.* teach the use of ASCA and ANCA in stratifying Crohn's disease in patients. There is certainly no mention of IgA anti-I2 antibodies or IgA anti-OmpC antibodies and their use in assessing risk of various subtypes.

Landers *et al.* aim was to assess the response to various antigens in Crohn's patients and the results showed that eighty-five percent responded to at least 1 antigen; and only 4% responded to all 4, whereas with microbial antigens, 78% responded to at least 1, 57% were double positive, but only 26% responded to all 3 (Abstract). The currently claimed methods for determining a risk of having or developing a clinical subtype of Crohn's disease are not taught or suggested.

B. Algorithm

In addition to the foregoing differences with respect to biomarkers, the currently claimed method recites unique method steps or an "algorithm," not taught or suggested by the cited art. The methods recite: a high magnitude of the three markers indicates a first risk; a high magnitude of exactly two of the three markers indicates a second risk; a high magnitude of exactly one of the three markers indicates a third risk; and the absence of a high magnitude of the three markers indicates a fourth risk. The unique "algorithm" is not obvious in view of the cited art.

In assessing the differences between the cited art and the claims at issue it is apparent that the references do not teach or suggest all the claim limitations. Moreover, at the time of the invention, an ordinary skilled artisan would not have found the differences in the claimed invention obvious. Applicants assert that the cited art does not teach or suggest all the claim limitations and therefore, a *prima facie* case of obviousness simply has not been established. In view of the foregoing, Applicants respectfully request that the Examiner withdraw the rejection.

II. REJECTION UNDER 35 U.S.C. § 112, FIRST PARAGRAPH

The Examiner has rejected claims 25-26 and 29-36 under 35 U.S.C. § 112, first paragraph, as allegedly containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention. In response, Applicants respectfully traverse the rejection.

The Examiner alleges that the claims recite limitations that were not clearly disclosed in the specification and recited in the claims as originally filed in the priority application. Applicants respectfully traverse the rejection.

Applicants recite a method of obtaining a sample from the subject, and determining the level of three markers in the subject, *i.e.*, IgA anti-I2 antibodies, anti-*Saccharomyces cerevisiae* antibodies (ASCA), and IgA anti-OmpC antibodies. This embodiment is clearly recited on page 28, lines 1-9, of U.S. Application No. 10/413,501, ("the '501 application") filed April 11, 2003, wherein it states:

> A method of the invention for diagnosing or predicting susceptibility to a clinical subtype of Crohn's disease in a subject having Crohn's disease by determining the presence or absence of IgA anti-I2 antibodies in the subject can *optionally* include the additional step of determining the presence or absence in the subject of a NOD2 variant, anti-Saccharomyces cerevisiae antibodies, IgA anti-OmpC antibodies, or perinuclear anti-neutrophil cytoplasmic antibodies (pANCA).

In the embodiment as currently claimed, anti-I2, anti-ASCA and anti-OmpC are determined, and therefore included, whereas NOD2 and anti-pANCA remain optional.

Further support for the claimed embodiments is found, for example, at page 6, lines 1-25 of the '501, wherein it states:

> As disclosed herein, IgA antibodies to I2 were present in 56.5% of the Crohn's disease patients in the study (see Example I). Patients expressing IgA anti-I2 antibodies were significantly more likely to have a fibrostenotic subtype of Crohn's disease than those not expressing IgA anti-I2 antibodies (71.4% vs. 43.3%, $p<0.001$) and significantly more likely to require small bowel surgery (66.7% vs. 37.1%, $p<0.001$). In addition, IgA anti-I2 antibody expression was negatively associated with ulcerative colitis-like Crohn's disease (20.6% vs. 41.24%, $p<0.001$). Quartile analyses revealed that higher levels of IgA anti-I2 antibodies were more strongly associated with the fibrostenotic subtype of Crohn's disease (p for the trend<0.001) and small bowel involvement (p-0.023), and inversely associated with ulcerative colitis-like Crohn's disease ($p=0.005$) compared to lower levels of IgA anti-I2 antibodies. In addition, as disclosed in Example I, conditional analysis performed on NOD2 variants and ASCA indicated that IgA anti-I2 antibodies were independently associated with the fibrostenotic subtype ($p=0.001$ and $p=0.005$, respectively). Similarly, IgA anti-I2 was independently associated with small bowel surgery when conditioned on NOD2 variation ($p=0.001$) or ASCA ($p=0.002$). These results indicate that the presence of IgA anti-I2 antibodies can be used to diagnose or predict susceptibility to a clinical subtype of Crohn's disease, such as the fibrostenotic subtype, in a subject having Crohn's disease.
>
> As further disclosed in Example I, patients with all three markers, IgA anti-I2 antibodies, one of the three NOD2 variants, and ASCA showed the greatest risk of the fibrostenotic subtype of Crohn's disease (82%, odds ratio=9.7, $p<0.000001$), compared with patients with two markers (74%, odds ratio=6.0), one marker (48%, odds ratio=1.9), or none of these markers (33%, odds ratio=reference group). These results indicate that the presence of IgA anti-I2 antibodies in combination with the presence of other markers can be used to diagnose or predict susceptibility to a fibrostenotic subtype Crohn's disease in a patient having Crohn's disease.

The foregoing disclosure clearly shows that the greatest risk occurs with three markers, compared to two markers or with one marker. Quartile analysis was also performed and supports dependent claims.

Moreover, Applicants had clear support for OmpC antibodies as disclosed in the '501 application at the bottom of page 48, lines 25-30, bridging to page 49 at the top:

> IgA anti-OmpC antibodies are another marker useful for determining a clinical subtype of Crohn's disease in a method of the invention. *IgA anti-OmpC antibodies are associated with the fibrostenotic subtype, need for small bowel surgery, and internal perforating disease subtype, and can be independently associated with the internal perforating disease subtype.* Provided herein is a method of diagnosing or predicting susceptibility to a clinical subtype of Crohn's disease in a subject having Crohn's disease by determining the presence or absence of IgA anti-OmpC antibodies in the subject, where the presence of IgA anti-OmpC antibodies indicates that the subject has a clinical subtype of Crohn's disease. In one embodiment, the clinical subtype of Crohn's disease is the fibrostenotic subtype. In another embodiment, the clinical subtype of Crohn's disease is the internal perforating disease subtype.
>
> The presence of IgA anti-OmpC antibodies in a subject can indicate that the subject has a fibrostenotic subtype of Crohn's disease. ***In some cases, the presence of IgA anti-OmpC antibodies can correlate with the presence of ASCA. In some embodiments, the presence of IgA anti-OmpC antibodies and ASCA are determined, while in other embodiments the presence of IgA anti-OmpC antibodies can be used as a surrogate marker for the presence of ASCA***. [Emphasis added].

Applicants had clear disclosure in the '501 application that in certain instances, *IgA anti-OmpC antibodies correlate with ASCA*. As is shown in Table 6 of the *current specification*, there is an increased likelihood of developing Crohn's disease characterized by fibrostenosing, internal perforating and small bowel surgery when an individual has immune reactivity to exactly "1," "2," or "3" markers.

Table 6
Disease Characteristics in Patients with Antibody Reactivity
Towards Microbial Antigens

Clinical Phenotype	# Antibodies Towards Microbial Antigens[1]				*ptrend*	OR (3 vs 0)	95% CI (3 vs 0)
	0	1	2	3			
Small Bowel Disease (%)	63.9	78.8	85.1	86.7	0.001	3.7	1.6-8.5
Fibrostenosing (%)	23.0	50.0	66.7	72.0	<0.001	8.6	4.0-18.9
Internal Perforating (%)	27.9	27.5	42.5	58.7	<0.001	3.7	1.8-7.6
Small Bowel Surgery (%)	23.0	50.0	57.5	72.0	<0.001	8.6	4.0-18.9
UC-Like (%)	42.6	27.5	24.1	10.7	<0.001	0.2	0.1-0.4

Rows: Numbers represent % of patients with a specific disease phenotype in the first four columns.

[1] Microbial antigens (I2, OmpC, and oligomannans); results irrespective of pANCA and NOD2/CARD15 status.

With regard to the *magnitude and number* of markers further support is found, for example, on page 16, lines 19-31, bridging to page 17 at the top of the '501 application, wherein it states:

> The requirement for small bowel surgery in a subject with the fibrostenotic subtype of Crohn's disease can indicate a more aggressive form of this subtype. As shown in Example I, patients expressing IgA anti-I2 antibodies were significantly more likely to have the fibrostenotic subtype of Crohn's disease and significantly more likely to require small bowel surgery than those not expressing IgA anti-I2 antibodies. In addition, **the amplitude or level of IgA anti-I2 antibodies in a subject can be correlated with the likelihood of having a particular clinical subtype of Crohn's disease. As shown in Example I, quartile analyses revealed that higher levels of IgA anti-I2 antibodies were more strongly associated with the fibrostenotic subtype of Crohn's disease and small bowel involvement and were negatively associated with**

ulcerative colitis-like Crohn's disease than were lower levels. Furthermore, the greater the number of fibrostenotic markers that a subject possesses, the greater chance that the subject will have an aggressive form of the fibrostenotic subtype of Crohn's disease requiring small bowel surgery (see Example I). For example, a subject with two or more markers can have a more severe form of the fibrostenotic subtype than a patient with one marker.

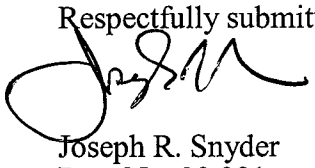
The foregoing support from the '501 application conveys with *reasonable clarity* to those skilled in the art that, as of the filing date sought, Applicants were in possession of the invention as now claimed. As the Examiner is well aware, and in accordance with MPEP § 2163.02, the subject matter of the claim need not be described literally (i.e., using the same terms or *in haec verba*) in order for the disclosure to satisfy the description requirement. It is clear that Applicants were in possession of the invention as now claimed. 35 U.S.C. § 112, first paragraph requires no more. As such, Applicants respectfully request that the Examiner withdraw the rejection and send this application to issue.

CONCLUSION

In view of the foregoing, Applicants believe all claims now pending in this Application are in condition for allowance. The issuance of a formal Notice of Allowance at an early date is respectfully requested.

If the Examiner believes a telephone conference would expedite prosecution of this application, please telephone the undersigned at 925-472-5000.

Respectfully submitted,



Joseph R. Snyder
Reg. No. 39,381

TOWNSEND and TOWNSEND and CREW LLP
Two Embarcadero Center, Eighth Floor
San Francisco, California 94111-3834
Tel: 925-472-5000
Fax: 925-472-8895
61313863 v1